REMARKS

Claims 38-58 were pending in the application. Claims 38-58 have been canceled without prejudice herein. New claims 59-92 have been added.

No new matter has been added. Support for claim 59 can be found at least in claims 53 and 55. In addition, support for the language "an amino acid sequence of at least 8 amino acids in length" can be found at least at page 12, line 18. Support for the language "comprising a nucleotide sequence corresponding to SEQ ID NO:1 and translated in a reading frame corresponding to the reading frame of SEQ ID NO:1 and +1 to the standard HCV reading frame" can be found at least at page 7, lines 14-23. Support for the language "or antigen binding portion thereof" can be found at least at page 21, lines 15-25. Support for the language "under conditions where the polypeptide and the antibody or antigen binding portion thereof can bind, determining the presence or absence of the polypeptide wherein presence of the polypeptide indicates infection with HCV" can be found at least at page 30, lines 1-14.

Support for claim 76 can be found at least in claims 53 and 55. In addition, support for the language "an amino acid sequence of at least 8 amino acids in length" can be found at least at page 12, line 18. Support for the language "comprising a nucleotide sequence shown in SEQ ID NO:1 and translated in a reading frame +1 to the standard HCV reading frame" can be found at least at page 11, lines 22-24. Support for the language "or antigen binding portion thereof" can be found at least at page 21, lines 15-25. Support for the language "under conditions where the polypeptide and the antibody or antigen binding portion thereof can bind, determining the presence or absence of the polypeptide wherein presence of the polypeptide indicates infection with HCV" can be found at least at page 30, lines 1-14.

Support for claims 60 and 77 can be found at least in claim 40.

Support for claims 61 and 78 can be found at least at page 2, line 17.

Support for claims 62 and 79 can be found at least in claim 58.

Support for claims 63 and 80 can be found at least in claim 41.

Support for claims 64 and 81 can be found at least in claim 44.

Support for claims 65 and 82 can be found at least at page 10, line 10.

Support for claims 66 and 83 can be found at least in claim 45.

Support for claims 67 and 84 can be found at least in claim 47.

Support for claims 68 and 85 can be found at least in claim 48.

Support for claims 69 and 86 can be found at least in claim 48 and 49.

Support for claims 70 and 87 can be found at least in claim 50.

Support for claims 71 and 88 can be found at least in claim 51.

Support for claims 72 and 89 can be found at least at page 24, line 8 to page 25, line 6.

Support for claims 73 and 90 can be found at least at page 30, lines 12-14.

Support for claims 74 and 91 can be found at least at page 9, lines 11-23.

Support for claims 75 and 92 can be found at least at page 30, lines 15-25.

Cancellation of and/or amendment to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in another patent application.

No additional search is required and no new issues have been raised by the amendments made herein. Furthermore, in view of the amendments and arguments set forth herein, the number of issues for appeal has been reduced. Therefore, the claim amendments made herein are permissible under 37 C.F.R. §1.116 as reducing the number of issues for appeal, and Applicants respectfully request that the present Amendment be entered.

Interview

Applicants thank the Examiner for the courtesy of a personal interview that took place on 9 May, 2005 between Applicants' Attorneys, Giulio DeConti and Megan Williams; and Examiners T. Brown and U. Winkler and Supervisory Examiner J. Housel. A Statement of the Substance of the May 9, 2005 Interview is being filed concurrently herewith.

Improper Finality of Office Action

The Examiner makes the action final. However, it is Applicants' position that the finality of the present Office Action is improper for the reasons set forth below.

"Under present practice, second or any subsequent actions on the merits shall be final, except when the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the new claims nor based on the information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97 with a fee with

the fee set forth in 37 CFR 1.17 (p)." MPEP 706.07. Applicants submit that the ***new grounds of rejection were not necessitated by amendments***, but rather the Examiner improperly made this Office Action final where new grounds of rejection that could have been raised in the previous Office Action were made. More specifically, the Feucht reference was not previously cited against the pending claims.

Accordingly, Applicants respectfully request that the finality of the Office Action be withdrawn pursuant to MPEP 706.07(d). If the Examiner is not persuaded by these Remarks to remove the finality of the rejection, Applicants reserve the right to petition the finality of the rejection.

The Pending Claims

The pending claims all depend from new claims 59 or 76. New claim 59 is directed to a method of diagnosing Hepatitis C virus (HCV) infection, comprising contacting a biological sample from a subject with ***an antibody or antigen binding portion thereof that specifically binds to a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by an HCV nucleic acid molecule comprising a nucleotide sequence corresponding to SEQ ID NO:1 and translated in a reading frame corresponding to the reading frame of SEQ ID NO:1 and +1 to the standard HCV reading frame***, under conditions where the polypeptide and the antibody or antigen binding portion thereof can bind, determining the presence or absence of the polypeptide wherein presence of the polypeptide indicates infection with HCV. As set forth, e.g., at page 7 lines 14-23 of the specification this language covers HCV sequences from the core region from isolates other than AF011751 (shown in SEQ ID NO:1) which are read in the same reading frame as SEQ ID NO:1, +1 to the standard reading frame.

New claim 76 is directed to a method of diagnosing Hepatitis C virus (HCV) infection, comprising contacting a biological sample from a subject with ***an antibody or antigen binding portion thereof that specifically binds to a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by a nucleic acid molecule comprising a nucleotide sequence shown in SEQ ID NO:1 and translated in a reading frame +1 to the standard HCV reading frame*** under conditions where the polypeptide

and the antibody or antigen binding portion thereof can bind, determining the presence or absence of the polypeptide, wherein presence of the polypeptide indicates infection with HCV.

Thus, the claims do not embrace any and all HCV alternate reading frame polypeptides, but only those comprising an amino acid sequence encoded by a nucleotide sequence corresponding to the core region shown in SEQ ID NO:1 or comprising an HCV amino acid sequence encoded by a nucleotide sequence shown in SEQ ID NO:1.

Rejection of Claims 52, 53, 55, 57, 58, and 38-49 Under 35 U.S.C. 112, First Paragraph

Enablement

The Examiner has rejected claims 52, 53, 57, 58, and 38-49 as not being enabled. This rejection is respectfully traversed as it may be applied to the new claims.

The Examiner indicates that "[t]he invention does not include the critical steps of introducing a sample, incubating the sample to obtain a detectable complex, or correlating the detected complex with HCV infection." Applicants note that the pending method claims need not set forth all the steps of the method where the metes and bounds of the invention would be clear to one of ordinary skill in the art. Moreover, the teachings of Applicants' specification clearly enable the skilled artisan to perform an assay according to the claims (see, e.g., pages 28-30 of the application). However, in the interest of expediting prosecution of the application, new claims 59 and 76 include these steps.

The Examiner further states that "the invention diagnoses HCV based on the detection of any and all immunogenic HCV ARF polypeptides."

In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra. Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the methods claimed without undue experimentation.

As set forth above, the claims require that the antibody used for detection specifically bind ***a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by an HCV nucleic acid molecule comprising a***

nucleotide sequence corresponding to SEQ ID NO:1 and translated in a reading frame corresponding to the reading frame of SEQ ID NO:1 and +1 to the standard HCV reading frame, or specifically bind ***to a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by a nucleic acid molecule comprising a nucleotide sequence shown in SEQ ID NO:1 and translated in a reading frame +1 to the standard HCV reading frame.*** Thus, the claims do not embrace any and all HCV alternate reading frame polypeptides, but only those comprising an HCV amino acid sequence encoded by a nucleotide sequence corresponding to the core region shown in SEQ ID NO:1 or comprising an HCV amino acid sequence encoded by a nucleotide sequence shown in SEQ ID NO:1.

Applicants provide extensive guidance to the skilled artisan to enable the claimed invention. For example, polypeptides within the scope of the claims are disclosed in the specification and variants of such polypeptides could be readily made by one of skill in the art using known methods. Applicants also teach how to make antibodies which recognize alternate reading frame polypeptides that could be used in the claimed assays to detect such polypeptides. In fact, such antibodies have been made by Applicants using the described methods. It is also clear from the working examples presented in the application (see e.g., Example 1 in which antibodies to alternate reading frame peptides were detected in HCV infected individuals using an ELISA assay) that immunogenic alternate reading frame polypeptides are made during infection with HCV.

In addition, the task of screening antibodies for their ability to react with alternate reading frame polypeptides does not constitute undue experimentation. "The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. . . . Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

In addition, the level of skill in the art with respect to biotechnology inventions has been found by the Court of Appeals for the Federal Circuit to be high. With respect to detection of HCV polypeptides, Applicants note that the state of the art with respect to detection of HCV is quite high. Standard HCV reading frame polypeptides are currently detected despite the genetic variation that exists between isolates. Applicants previously provided evidence of such routine detection standard immunochemistry (see, e.g., the Walker reference provided as Appendix C

with the response filed January 5, 2003). It would not require undue experimentation to detect the presently claimed HCV alternate reading frame sequences given the teachings of the specification.

In sum, Applicants' disclosure provides sufficient direction and guidance as to how to practice the invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known. Accordingly, Applicants request reconsideration and withdrawal of the foregoing rejection.

Written Description

The Examiner has rejected claims 52, 53, 55, 57, 58, and 38-49 as failing to comply with the written description requirement. This rejection is respectfully traversed as it may be applied to the presently pending claims.

The Examiner states that "Applicants' specification does not disclose a method for diagnosing HCV infection that omits the steps of introducing a sample, incubating the sample to obtain a detectable complex, and correlating the detected complex with HCV infection." Applicants point out that support for the claim as previously pending can be found in the specification as filed. However, as set forth above, new claims 59 and 76 include these steps.

The Examiner further states that this specification does not disclose the full range of ARF polypeptides claimed. The Examiner also states that the specification also discloses only a limited number of purportedly immunogenic sequences. These comment is also traversed.

In determining whether the Written Description requirement is met, the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" published in the Federal Register on January 5, 2001 state that the Examiner should:

> compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (citing to Wang Labs v. Toshiba Corp., (Fed. Cir. 1993) 993 F.2d 858, 865). . . . Information which is well known in the art need not be described in detail in the specification. (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380).
>
> Page 1105.

At page 1106, the Guidelines further state that "[t]he description need only describe in detail that which is new or not conventional (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380).

As set forth above, the claims require that the antibody or antigen binding portion thereof used for detection specifically bind ***a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by an HCV nucleic acid molecule comprising a nucleotide sequence corresponding to SEQ ID NO:1 and translated in a reading frame corresponding to the reading frame of SEQ ID NO:1 and +1 to the standard HCV reading frame***, or specifically bind ***to a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by a nucleic acid molecule comprising a nucleotide sequence shown in SEQ ID NO:1 and translated in a reading frame +1 to the standard HCV reading frame.*** Thus, the claims do not embrace any and all HCV alternate reading frame polypeptides, but only those comprising an amino acid sequence encoded by a nucleotide sequence corresponding to the core region shown in SEQ ID NO:1 or comprising an HCV amino acid sequence encoded by a nucleotide sequence shown in SEQ ID NO:1.

Applicants describe a genus of alternate reading frame polypeptides expressed by HCV nucleic acid molecules translated in alternate reading frames. Applicants teach that alternate reading frame polypeptides comprise epitopes that are translated from an HCV nucleic acid molecule, but rather than being read in the standard open reading frame, are translated from a reading frame which is, e.g., +1 to the standard HCV open reading frame. Applicants teach how one of skill in the art could take any HCV nucleic acid sequence and shift it into an alternate reading frame to obtain the amino acid sequence of an alternate reading frame polypeptide, e.g., by using the an alternate reading frame of the ***known HCV isolate*** having GenBank accession number AF011751 as a reference sequence (see, e.g., page 5 of the specification). A portion of the AF011751 nucleic acid sequence encoding an exemplary alternate reading frame polypeptide was provided as an example in Applicants specification. Given Applicants teachings, one of ordinary skill in the art could determine the nucleotide sequence encoding an alternate reading frame polypeptide by simply shifting the reading frame +1 to the standard ORF and, using the genetic code, obtain the amino acid sequence of an alternate reading frame polypeptide sequence.

Numerous HCV nucleic acid molecules were well known and publicly available in the art at the time the application was filed. As set forth above, according to the Written Description Guidelines, known conventional information (such as known HCV nucleic acid sequences) need not have been described in Applicants specification (see, e.g., Written Description Guidelines pages 1105 and 1106). Applicants submit that the exemplary known AF011751 nucleic acid sequence provided in the specification was sufficient to describe the genus of HCV nucleotide sequences. In addition, HCV nucleic acid sequences are all structurally related. Although there may be some variability among HCV nucleotide sequences, all such sequences are genetic information for HCV and not for other viruses and they comprise common features possessed by all HCV nucleic acid molecules as distinguished from other viruses.

In addition, Applicants provided examples of other exemplary alternate reading frame polypeptides based on the nucleotide sequence of exemplary published HCV isolates AF011751, D17763, D10988, D14853, D00944, D63822, Y1604, and D50482 (see Table 1). Applicants developed a consensus (majority) alternate reading frame polypeptide sequence based on homology observed among alternate reading frame polypeptide sequences based on alternate reading frame translation of known HCV nucleic acid sequences (shown in Table 1). Applicants further demonstrated that such alternate reading frame polypeptides are expressed in the cells/fluids of patients with various strains of HCV by demonstrating that antibodies reactive with the consensus peptide were detected in such patients.

Moreover, Applicants note that USSN 60/089138, incorporated by reference into the instant application at page 35 and to which the instant application claims priority, contains examples of additional nucleic acid sequences encoding alternate reading frame polypeptides. Specifically, Appendix A and B filed with that application contain 42 pages each which list the GenBank Accession numbers and nucleotide sequences of the core region of other exemplary HCV isolates corresponding to SEQ ID NO:1. Appendix A contains sequences identified based on homology to the core region of the AF011751 isolate and Appendix B contains sequences obtained using the first nucleotide of the +1 alternate reading frame as the first nucleotide of the sequence.

Given the description in the specification, one of ordinary skill in the art would have known that Applicants were in possession of the claimed invention. Armed with the knowledge of publicly available HCV nucleic acid sequences, the genetic code, and the benefit of

Applicants teachings, one of ordinary skill in the art would have immediately understood that Applicants were in possession of at least hundreds of examples of alternate reading frame polypeptides. Moreover, based on the fact that antibodies to a consensus alternate reading frame polypeptide were detected in HCV patients, one of ordinary skill in the art would have understood that Applicants were in possession diagnostic methods for detection of a genus of polypeptides or antibodies reactive with such polypeptides.

Applicants further point out that an appropriate claim scope is necessary to adequately protect Applicants' invention from those who could make a minor change to an HCV nucleic acid sequence or HCV alternate reading frame polypeptide amino acid sequence based on Applicants' broad teachings to avoid infringement while exploiting the benefits of Applicants' invention. To deny a claim of appropriate scope would serve to carve a pathway around the claims requiring no inventive contribution.

As the pending claims are enabled and adequately described, Applicants respectfully request that the rejection of claims 52, 53, 55, 57, 58, and 38-49 under 35 USC § 112, first paragraph be reconsidered and withdrawn.

Rejection of Claims 52-55 and 38-49 Under 35 U.S.C. 112, second paragraph

The Examiner has rejected claims 52-55 and 38-49 Under 35 U.S.C. 112, second paragraph. This rejection is respectfully traversed.

The Examiner states that claim 52 is indefinite for omitting essential steps. As set forth above, claim 52 has been canceled and new claims 59 and 76 include these steps.

The Examiner further states that claim 52 is indefinite in the recitation of "a polypeptide comprising . . . an HCV alternate reading frame polypeptide." The Examiner contends that this limitation is indefinite because it is unclear which polypeptides are encoded by such a reading frame." The Examiner continues, "[s]ince the polypeptide 'comprises' and [sic] alternate reading frame polypeptide, does the claimed invention also include missense, non-sense and/or silent mutations?" Claim 52 has been canceled. It is Applicants position that claims 59 and 73 are clear in the that the term "comprising" means that the molecule could comprise additional an additional amino acid sequence.

The Examiner finds claim 57 indefinite in the recitation of "60% to 70% identical to a polypeptide sequence shown in SEQ ID NO:2." The Examiner states that it "is unclear whether

'a polypeptide' refers to a polypeptide consisting of, or comprising, SEQ ID NO:2." This rejection has been obviated by the cancellation of claim 57.

The Examiner also finds claims 57, 58, 39, 40, 42, and 43 indefinite in the recitation of "at least about." The Examiner states that "the specification does not provide any guidance to the scope of the term. Although Applicants traverse these remarks on the grounds that the metes and bounds of the claim would be clear on one of ordinary skill in the art, in the interest of expediting prosecution, these claims have been canceled.

Prior Art

Rejection of Claims 52, 53, 55, 58, 38-41 and 46 Under 35 U.S.C. 102(b) As Being Anticipated by Lo 1995.

The Examiner has rejected claims 52, 53, 55, 58, 38-41 and 46 as being anticipated by Lo 1995. This rejection is respectfully traversed as it may be applied to the new claims.

As set forth above, the claims require that the antibody or antigen binding portion thereof used for detection specifically bind ***a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by an HCV nucleic acid molecule comprising a nucleotide sequence corresponding to SEQ ID NO:1 and translated in a reading frame corresponding to the reading frame of SEQ ID NO:1 and +1 to the standard HCV reading frame***, or specifically bind ***to a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by a nucleic acid molecule comprising a nucleotide sequence shown in SEQ ID NO:1 and translated in a reading frame +1 to the standard HCV reading frame.***

The Lo 1995 reference confirms the teaching of Lo 1994 (also referred to as Lo B1 in previous Office Actions) and states that P16 and P21 are co-amino-terminal (see page 459, column 1, paragraph 2). The amino terminal sequence of P16 is taught to be: XTNPKPQK$_9$KNKRNTN, identical to the P21 sequence (see Table 1). According to this teaching, p16 is encoded by the standard HCV reading frame which specifies the core protein and, therefore, is not an alternate reading frame polypeptide. The reference also examines expression of plasmids comprising HCV core protein sequence in the presence or absence of its

downstream E1 envelope protein sequence and teaches that P16 is the major core protein product when the HCV-1 core gene is expressed in the absence of its down-stream E1 envelope protein (see page 460, column 1, paragraph 4). In addition, the reference teaches that P16 is expressed in the nucleus of cells (see page 456, column 1, paragraph 2).

In summary, the Lo 1995 reference (and the previously cited Lo 1994 reference) teach that P16:

i) has a molecular size of p16;

ii) is a truncated version of core protein;

iii) contains 16 amino acids of core;

iv) is recognized by antibody against the core protein;

v) accounts for 100% of the polypeptide produced in in vitro translation assays; and

vi) localizes in the nucleus.

The Xu 2001 reference (cited by the Examiner as revealing "that Lo's P16 was in fact an HCV ARF polypeptide") teaches a polypeptide with ***distinctly different*** characteristics than those characteristics of P16. First, the P17 polypeptide taught by Xu et al. is of a different molecular size than P16, i.e., P17 rather than P16 (see Figure 1). Second, the Xu protein is taught to be a chimeric protein, comprising both core amino acid sequences and alternate reading frame sequences. The Xu protein is stated to be produced as a result of ribosomal frameshifting. Therefore, in contrast to P16, P17 it is not a truncated version of the core protein. Third, the Xu P17 polypeptide is taught to contain only about 10 or 11 amino acids of the core protein covalently linked to about 150 amino acids encoded in the +1 alternate reading frame (see Figure 3 and page 3844, column 2). Therefore, P17 has a different amino acid sequence than P16, which is taught by Lo to contain at least 16 amino acids of the core protein. Thus, P16 contains amino acids of the core protein that are not present in P17, i.e., core amino acids 12 to 16. Fourth, the P17 polypeptide is expressed in the cytoplasm. Four of the authors of the Xu 2001 paper authored a paper which teaches that P17 (F protein) is expressed in the cytoplasm (see Xu 2003 "Hepatitis C Virus F Protein is a Short-Lived Protein Associated with the Endoplasmic Reticulum" Journal of Virology 77:1578; attached as Appendix A to the Response filed January 5, 2003, e.g., at p. 1580), whereas P16 was taught by Lo to be expressed in the nucleus. Roussel et al (Characterization of the expression of the hepatitis C virus F protein" Journal of General Virology, 2003, 84, 1751-1759; attached as Appendix B to the Response filed January 5, 2003)

also report that P17 (F-protein) localizes to the cytoplasm (Figure 6, page 1756). Finally, the P17 polypeptide of Xu et al. 2001 is expressed as about 30% of in vitro product in a reticulocyte lysate assay (see Fig. 2, lane B1). On page 3846 Xu et al., EMBO J, 2001 state that the efficiency of ribosomal frameshifting is "~30% in vitro." This is in contrast to the finding that P16 is expressed as 100% of the product made in a reticulocyte lysate assay by the same laboratory and published in Lo 1994.

In contrast to Lo 1995, Xu teaches that P17

i) has a molecular size of p17;

ii) is a chimeric protein comprising sequences of core and ARF sequences;

iii) contains 10-11 amino acids of core;

iv) accounts for 30% of the polypeptide produced in in vitro translation assays; and

v) localizes in the cytoplasm.

Thus, there are distinct differences between the P16 polypeptide of Lo 1995 and the P17 (F protein) polypeptide taught by Xu et al. In order to establish inherency "the extrinsic evidence must make clear that the missing descriptive matter is ***necessarily*** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill (emphasis added)." Harmon. R. L. "Patents in the Federal Circuit (6^{th} Edition, Bureau of National Affairs, Inc. 2003). The Xu reference fails to establish that P16 and P17 are necessarily the same and, therefore, the prior art of record fails to teach or suggest alternate reading frame polypeptides as presently recited in the claimed methods.

In addition, even if P16 were an alternate reading frame protein, which Applicants deny has been established, one faced with the problem of improving HCV diagnostics at the time the invention was made would not have recognized it as such and would not have known that polypeptides encoded in their entirety or in part in the alternate reading frames of HCV or antibodies that recognize them could be used to diagnose HCV infection.

Moreover, the pending claims are directed to ***methods of diagnosing HCV infection***. The Lo 1995 reference fails to teach or suggest methods of diagnosing HCV infection comprising detecting the presence or absence of P16 or an antibody reactive therewith. The reference does not teach that P16, regardless of whether or not it is an alternate reading frame polypeptide, is expressed in during the course of HCV infection. ***All of the data in the reference***

was generated using in vitro translation experiments. In addition, the reference teaches that P16 is only detected in ***one isolate*** tested, the HCV-1 isolate, which has a Lys-9 residue. A second closely related isolate, RH, was tested and it ***did not*** yield P16. Lo B1 considered expression of P16 to be dependent on the sequence of the HCV-1 isolate and they identified a highly unusual feature of the HCV-1 sequence—the Lys-9 codon, as a key contributor to P16 production. The limited expression of P16 taught in the reference ***teaches away*** from the use of P16 as a diagnostic.

Similarly, the Lo 1995 reference fails to teach or suggest methods of diagnosing HCV infection comprising detecting the presence or absence of an alternate reading frame polypeptide or antibodies reactive therewith. The reference looks at expression of P16 from artificial constructs and teaches that P16 is expressed from these constructs in *E. coli* and CV1 cells. However, expression of P16 is taught to be enhanced ***in the absence*** of the E1 envelope protein. In the case of infection with HCV, the E1 envelope protein is present. The reference does not examine the expression of P16 in the course of HCV infection and there is no indication in the reference that P16 is made during infection.

Prior to Applicants invention, ***i) no one had identified alternate reading frame polypeptides having an amino acid sequence that differed from core, ii) no one had shown that such polypeptides were produced during an infection in a human subject, and iii) no one had shown that such polypeptides were immunogenic in a human subject.*** Absent Applicants teachings, there was no motivation present in the art to diagnose HCV infection by detecting the presence or absence of a polypeptide comprising an amino acid sequence encoded by an HCV alternate reading frame or antibodies reactive therewith. In fact, the Xu 2001 reference, cited by the Examiner and filed after Applicants filing date, clèarly states that based on the earlier work of others (including Lo 1995) whether the P16 or the F protein could be synthesized during natural HCV infection in patients was "***unclear***" (see Xu 2001, page 3844, column 1, paragraph 2). In contrast to the teachings of the prior art, Applicants have shown that alternate reading frame polypeptides are produced during infection and that they are immunogenic. Applicants provide a working example in which alternate reading frame polypeptides were synthesized and sera from patients with HCV were tested for their reactivity with the polypeptides. These data show that HCV patient sera contained antibodies reactive with alternate reading frame polypeptides.

Moreover, at the time the invention was made there was no reasonable expectation of success that HCV could be diagnosed using P16 or antibodies reacting therewith. There was no evidence that P16 had any epitopes that differed from the epitopes present in the core protein. In fact, the only antibodies reported by Lo 1994 and Lo 1995 to react with P16 were anti-core antibodies, not antibodies to epitopes encoded in an alternate reading frame. In addition, Lo B1 teaches that Lys-9 was critical for P16 expression (see page 127, column 1, paragraph 2) and, given that HCV-1 is virtually the only isolate with Lys-9, Lo 1994 teaches that P16 is expressed by only one isolate. If Lys-9 were critical for P16 synthesis as concluded by the authors of Lo B1, HCV would not be expected to produce P16 during natural infections in humans except infections caused by HCV-1. In addition, Lo 1995 teaches that P16 expression from HCV-1 was *decreased* when the E1 envelope protein was present in the construct. Given that E1 is present in normal infection, this result implies that P16 might be an in vitro artifact. Therefore, absent Applicant's teachings, one of ordinary skill in the art would not have had a reasonable expectation of success in using the claimed methods to diagnose HCV infection.

Accordingly, the claims are not anticipated by the art of record and it is respectfully requested that this rejection be reconsidered and withdrawn. If the Examiner insists on maintaining this rejection Applicants respectfully request specific rebuttal of the above arguments be placed on the record.

Rejection of Claims 52 and 57 Under 35 U.S.C. 102(b) Over Feucht 1995

The Examiner has added a new grounds of rejection. Claims 52 and 57 have been rejected over Feucht 1995. This rejection is respectfully traversed to the extent that it may be applied to the new claims.

The Examiner states that Feucht "anticipates the claimed invention in that it teaches the serodiagnosis of HCV-infected individuals comprising detecting a protein that is 60% to 70% identical to a polypeptide sequence shown in SEQ ID NO:2 (see eg. Fig. 1 and Table 2)." However, this is not the case.

As set forth above, the claims require that the antibody or antigen binding portion thereof used for detection specifically bind ***a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by an HCV nucleic acid molecule comprising a nucleotide sequence corresponding to SEQ ID NO:1 and translated in a reading frame corresponding to the reading frame of SEQ ID NO:1 and +1 to the standard***

HCV reading frame, or specifically bind ***to a polypeptide comprising an amino acid sequence of at least 8 amino acids in length which amino acid sequence is encoded by a nucleic acid molecule comprising a nucleotide sequence shown in SEQ ID NO:1 and translated in a reading frame +1 to the standard HCV reading frame.***

Figure 1 of the Feucht reference illustrates the results of an immunoblot in which RNA isolated from the sera of HCV infected patients was amplified with primers for different regions of HCV polyprotein translated in the standard reading frame: core, SN3, NS4, and NS5. (See page 621 of the reference, column 1). The molecules detected are not ***polypeptides comprising an amino acid sequence encoded by a reading frame +1 to the standard HCV open reading frame*** as required by the pending claims but rather comprise amino acid sequences encoded by the standard HCV open reading frame. Accordingly, the reference fails to anticipate the claimed invention and Applicants request that the rejection be reconsidered and withdrawn.

CONCLUSION

If a telephone conversation with applicant's agent would expedite the prosecution of the above-identified application, the examiner is urged to call applicant's agent at (617) 227-7400.

Respectfully submitted,

Megan E. Williams
Registration No. 43,270
Attorney for Applicants

LAHIVE & COCKFIELD
28 State Street
Boston, MA 02109
(617) 227-7400

Dated: **May 19, 2005**